## REMARKS

Applicants thank Examiner Chunduru for the courtesy of arranging the interview with Examiner Fredman and also thank Examiner Fredman for agreeing to meet with Applicants in Examiner Chunduru's absence.. Claims 40-80 are cancelled herein. New claims 81-107 are now pending.

### I. New Claims 81-107

New claims 81-107, which include no new matter,1 reflect the understandings reached during the interview of December 9, 2003. The Interview Summary reads as follows:

> The invention was discussed. The ways in which it distinguished over Stemmer were considered. In particular, a limitation that prohibits polymerase would appear to overcome Stemmer, when in some steps.

As made clear at the Interview, the phrase "when in steps" reflects the recognition by the Patent Office that polymerase need not be excluded from all parts of the claimed method in order to overcome Stemmer. Indeed, Applicants believe that it is not necessary to expressly exclude polymerase from any part of the claimed method to overcome Stemmer. As described in Applicants' Amendment of April 15, 2003, the claimed method differs at its core from Stemmer.

Nevertheless, new claims 82-84, 106 and 107 expressly exclude or limit the use of polymerase. New claims 82 and 106 prohibit the use of polymerase altogether. New claims 83, 84 and 107 limit the use of polymerase to amplifying: the different polynucleotides, the cleavage fragments, the formed recombinant polynucleotide, or the assembly template. Applicants' intention in these claims is to limit the use of polymerase to increasing the number of copies of these sequences, thereby further emphasizing that the polymerase is not used for the actual recombination event.

Applicants' method of recombination relies primarily on ligation, whereas Stemmer's method of DNA shuffling relies entirely on polymerization. As such, Stemmer's

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[1] For example, with regard to claims 82-84, 106 and 107, support for limitations on the specific uses of a polymerase appear literally or implicitly in the application on page 1, lines 15-19; page 2, lines 4-12; page 3, lines 31-32; page 4, line 22-24; page 4, line 31 to page 5, line 4; page 7, lines 23 to page 8, line 2; page 9, lines 9-11; page 11, lines 2-24; pages 16-21; and Figure 5.

method is polymerase-mediated, not ligase-mediated. In Stemmer, a primer hybridizes to a template and is extended along the template with a polymerase until the extended primer copies the entire template. In other words, Stemmer's process mimics the natural strand switching process. Accordingly, Stemmer does not rely on ligation of hybridized fragments to actually form the recombinant polynucleotide. Stemmer uses a ligase only to seal the already-formed recombinant polynucleotide into a vector for cloning.

The present invention relies on making the ends of the fragments become adjacent to one other and therefore amenable to ligation. The ends of the fragments are made adjacent to one another through sheer repetition of the steps and optionally through filling in the gaps between hybridized fragments[2] or through the use of enzymes such as flap endonuclease to degrade the overlapping portions of hybridized fragments.

Applicants respectfully request withdrawal of all outstanding objections and rejections.

**II. Related Application**

Pursuant to the recent case *Dayco Products Inc. v. Total Containment Inc.*, 329 F.3d 1358 (Fed. Cir. 2003), patent applicants may now have a duty to inform examiners about rejections in related applications that are handled by different examiners. As such, please note that there was a rejection in a CIP application (09/840,861) of the above-captioned application. The claims of the CIP differ from the claims of the above-captioned application.[3] Furthermore, in view of a

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[2] Applicants' Amendment of April 15, 2003, states that the present invention does not encompass gap filling. That statement, which was flat wrong, was based on a technical misunderstanding on the part of Applicants' undersigned counsel. The present invention can encompass gap filling provided that the polymerase lacks strand-displacement activity and therefore only fills gaps between hybridized fragments rather than displacing the hybridized fragments and thereby copying the entire template. Of course, the new claims that expressly exclude polymerase or limit it to amplification do not encompass the use of polymerase for gap filling.

[3] Rejected claim 1 of the CIP application is as follows:

1. A method of creating at least one recombinant polynucleotide sequence, comprising:

(a) providing oligonucleotide fragments derived from an initial bank of at least two polynucleotide sequences;

(continued...)

recent interview with the Examiner of the CIP, Applicants' Amendment of December 29, 2003 in the CIP appears to overcome the rejection therein.

Respectfully submitted,
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(b) hybridizing the fragments to an assembly matrix so that the fragments are oriented for ligation with each other; and

(c) ligating the oriented fragments to form a recombinant polynucleotide sequence.